claim 18: page 6, lines 19-25; claim 36: page 5, lines 11-13; claim 37: page 5, lines 13-14; claim 38: page 8, lines 32-34; claim 39: page 8, lines 31-32; claim 40: page 8, lines 34-35 and page 9, lines 1-2; claim 41: page 9, line 2; claim 42: page 9, lines 2-3; claim 43: page 9, line 4; claim 44: page 9, line 4; claim 45: page 9, line 3. This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 1, 15-18 and 36-45 will be pending.

Priority

The Examiner stated that the applicant's claim for priority under 35 U.S.C. 120 is acknowledged. The Examiner alleged that U.S. Serial No. 08/592,070, filed January 26, 1996, and U.S. Serial No. 08/755,235, filed November 22, 1996, upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the claims of this application. The Examiner alleged that U.S. Serial No. 08/592,070 and U.S. Serial No. 08/755,235 do not support claims to methods to prevent accelerated development of atherosclerosis, or to inhibit progression of a macrovessel disease, which comprise administering the V-domain of sRAGE.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 1 which recites as follows: "A method of preventing atherosclerosis in a subject suffering from hyperlipidemia which comprises administering

to the subject a polypeptide which is an agent capable of inhibiting an interaction between AGE and RAGE in an amount effective to prevent atherosclerosis in the subject." Applicants contend that U.S. Serial No. 08/592,070 (hereinafter "'070 application"), filed January 26, 1996, and U.S. Serial No. 08/755,235(hereinafter "'235 application"), filed November 22, 1996 adequately support the pending claims.

In support, the '070 application recites in-part at page 11, lines 3-5, that the invention provides for a method of "inhibiting interaction of an amyloid-β peptide with a receptor for advanced glycation endproduct." Further, the '070 application recites in-part at page 13, lines 25-33, that "administering to the subject an agent capable of inhibiting the interaction of the amyloid-β peptide with the receptor for advanced glycation endproducts" treats conditions such as "diabetes" and "hyperlipidemic atherosclerosis." Since the claimed invention relates to a method of preventing atherosclerosis in a subject suffering from hyperlipidemia by administering an inhibitor of receptor for advanced glycation endproducts, the '070 application provides support for the claims. Thus, the claimed invention is entitled to an effective filing date of January 26, 1996 (i.e. the filing date of the '070 application).

In response to the Examiner's comments regarding a lack of support in the '070 and '235 application for claims inhibiting progression of a macrovessel disease, applicants without conceding the

correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 19-27, 29, 30 and 32-35 without prejudice or disclaimer to applicants' right to pursue the subject matter of this claim in a later-filed application. Claims 19-27, 29, 30 and 32-35 recite methods of inhibiting progression of macrovessel disease. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Continuation-in-part

The Examiner alleged that applicant has not specified how the parent cases are related to the instant application, i.e. if they are a continuation-in-part. The Examiner stated that the priority date for this application remains August 05, 1997, which is the filing date of application 08/905,709.

In response, applicants have amended the paragraph on page 1, lines 6-9, such that it now provides that the subject application is a continuation-in-part of U.S. Serial No. 08/592,070, filed January 26, 1996 and U.S. Serial No. 08/755,235, filed November 22, 1996. Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Confirmation of the Information Disclosure Statement

The Examiner stated that the Information Disclosure Statement (PTO

1449) has been received. The Examiner stated that as indicated on the IDS signed by the Examiner, some references have not been considered as they have not been provided by Applicants.

In response, applicants will send at a later date the references allegedly not received by the patent office, i.e. below listed references 2, 6, 7, 12, 17, 23 and 25. As confirmation of the information disclosure statement filed on May 11, 2001, and to ensure consideration of all references listed on Form PTO-1449, applicants list below all 32 references. Please note that copies of below listed references 1, 3-5, 8-11, 13-16, 18-22, 24 and 26-32 were provided in the information disclosure statement filed on May 11, 2001. Applicants understand that all below listed references, i.e. 1-32, will be considered upon receipt of the references allegedly not received by the patent office, i.e. below listed references 2, 6, 7, 12, 17, 23 and 25.

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vascular diseases. Science 272: 689-693.

4. Hori, et al. "The Receptor for Advanced Glycation Endproducts: Implications for the Development of Diabetic Vascular Disease. Fundam. Clin. Cardiol." In: The Endothelium in Clinical Practice. January 1997, Chapter 11, pages 311-329.

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8. Morser et al., U.S. Patent No. 5,864,018, filing date April 16, 1996.

9. Morser et al. PCT International Application No. PCT/EP97/01834, filed April 11, 1997, published October 23, 1997; Publication No. WO 97/39125, Antibodies Against the Advanced Glycation Endproduct Receptor and Uses Thereof.

10. Morser et al. PCT International Application No. PCT/EP97/01832, filed 11 April 1997, published October 23, 1997, Publication No. WO 97/39121, Advanced Glycation Endproduct Receptor Peptides and Uses Thereof.

11. Nakamura, Y. et al. (1993) Immunohistochemical localization of advanced glycosylation endproducts in coronary atheroma and cardiac tissue in diabetes mellitus. Am. J. Pathol. 143(6):1649-1656.

12. Nakashima Y, Plump A, Raines E, Breslow J, Ross R: ApoE-deficient mice develop lesions of all phases of atherosclerosis throughout the arterial tree. *Arterioscler Thromb* 1994;141:133-140.

13. Neeper, M., et al. (1992). Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J. Biol. Chem. 267: 14998-15004.

14. Palinski, W. et al. (1995) Immunological evidence for the presence of advanced glycation end products in atherosclerotic lesions of euglycemic rabbits. *Arterioscl. Thromb. And Vasc. Biol.* 15(5):571-582.

15. Park, L., et al. (1998) "Suppression of accelerated diabetic atherosclerosis by soluble Receptor for AGE (sRAGE)" *Nature Medicine*, 4:1025-1031.

16. Park, L., et al. (1997). A murine model of accelerated diabetic atherosclerosis: suppression by soluble receptor for advanced glycation endproducts. Circulation Supplement. Abstract 3079

17. Ritthaler, et al. (1995) Expression of receptors for advanced glycation end products in peripheral occulsive vascular disease. Am. J. Path. 146:688-694.

18. Schmidt, A. M. et al. (1993) Regulation of human mononuclear phagocyte migration by cell surface-binding proteins for advanced glycation end products. *J. Clin. Invest.* 92:2155-2168.

19. Schmidt, A. M., et al. (1997) "The V-Domain of Receptor for Advanced Glycation Endproducts (RAGE) mediates binding of AGEs: a novel target for therapy of diabetes" *Circulation Supplement*, 96:#194, p. I -37.

20. Schmidt, A-M, et al. (1994) "Cellular receptors for advanced glycation end products" *Arterioscler. Thromb.*, 14:1521-1528.

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interactions and gene activation in response to circulating AGE proteins" *Proc. Natl. Acad. Sci. (USA)*, 91:8807-8811.

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25. Stern, D., AM Schmidt and Jun Wu - PCT International Publication No. WO/98/22138 Published May 28, 1998, PCT International Application No. PCT/US97/21197 filed November 12, 1997 A Method For Treating Symptoms Of Diabetes In A Subject (Attny Dkt. 50159-PCT).

26. U.S. Patent No. 5,688,653, November 18, 1997 (Ulrich, et al.).

27. Vlassara et al., US Patent 5,585,344.

28. Vlassara, H., et al. (1995) "Identification of Galectin-2 as a high affinity binding protein for Advanced Glycation Endproducts (AGE): a new member of the AGE-Receptor complex" *Molecular Medicine*, 1:634-646.

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glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab. Invest. 70: 138-151.

30. Wautier, J. L., et al. (1996) "Receptor-mediated endothelial dysfunction in diabetic vasculopathy: sRAGE blocks hyperpermeability in diabetic rats" *J. Clin. Invest.*, 97 (1):238-243.

31. Wautier, J.-L., et al. (1996). Interaction of diabetic erythrocytes bearing advanced glycation endproducts with the endothelial receptor AGE induces generation of reactive oxygen intermediates and cellular dysfunction. Circulation Supplement 94(8): #4139.

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Claim Rejections under 35 U.S.C § 102(e)

The Examiner rejected claims 1-10, 12, 13, 15-27, 29, 30, 32-35 under 35 U.S.C. 102(e) as being anticipated by Morser, U.S. Patent No. 5,864,018. The Examiner stated that the claims are to methods which comprise administering a polypeptide comprising the V-domain of sRAGE or a derivative thereof capable of inhibiting the interaction of AGE and RAGE. The Examiner stated that Morser teaches peptides like the peptide of SEQ ID No:8, which block the

interaction of AGE and sRAGE (col.6, lines 41-52 and col.7, lines 13-20). The Examiner stated that while Morser defines these peptides by their sequence, these peptides constitute in fact fragments of sRAGE of about 10 amino acids in length, located in the V domain of sRAGE (see attached). The Examiner stated that the peptides of Morser are derivatives of the V-domain of sRAGE, as the specification, at page 8, line 30+, recites that: "The polypeptide may be a derivative of soluble receptor for advanced glycation end products (sRAGE). The Examiner stated that the polypeptide may be a soluble extracellular *portion of a receptor* for advanced glycation end product...". The Examiner stated that he teaches that the soluble peptides of the invention will comprise one of more of the Ig-like domains of the extracellular region of RAGE (col.5, lines 24-28), therefore the soluble extracellular domain (sRAGE), comprising one Ig V and two IgC domains, is envisioned. The Examiner stated that he teaches that these polypeptides are useful in treating or preventing disorders which result from excessive levels of AGEs (col.19, lines 1-24), in particular in diabetic microvasculopathy, occlusive vascular disorders and atherosclerosis. The Examiner stated that he teaches therapeutically effective amounts of the polypeptides, and methods of administration (col.19, line 48 continuing through col.20). The Examiner stated that claims 1-4, 8, 10, 13, 15-21, 25, 27, 30, 32-35 are anticipated. The Examiner stated that Claims 5-7, 9, 22-24, 26 are included in the rejections, as the methods apply to disorders that are associated with diabetes or macrovessel diseases. The Examiner stated that claims 12 and 29 are included

in the rejection, as the polypeptides of Morser encompass a 10 kilodalton domain of sRAGE. The Examiner stated that the peptides of SEQ ID No.: 18, 12, 13, and 5 are also fragments of sRAGE of about 10 amino acids in length, located in the V domain os sRAGE (see attached), able to block interaction of AGE and sRAGE. The Examiner stated that no claim is allowed.

In response, applicants respectfully traverse the Examiner's above rejection. The MPEP states that a rejection based on 35 U.S.C. 102(e) can be overcome by perfecting priority under 35 U.S.C. 120 by amending the specification of the application to contain a specific reference to a prior application. Applicants contend that the claimed invention is entitled to a priority date of January 26, 1996 as discussed supra at page 2. Therefore, since Morser, U.S. Patent No. 5,864,018 is only available as a reference as of August 16, 1996, i.e. after the effective filing date of the claimed invention (January 26, 1996), Morser is not available as a 102(e) reference. Applicants contend that the claimed priority date obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

12/28/01
John P. White Date
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